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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF PREVENTION, PESTICIDE AND TOXIC SUBSTANCES

OPP OFFICIAL RECORD
HEALTH EFFECTS DIVISION
SCIENTIFIC DATA REVIEWS
EPA SERIES 361

MEMORANDUM

October 8, 2009

SUBJECT: **Tetramethrin:** Response to Oral Benchmark Dose Analysis – Supplemental Submission.

PC Code: 069003
Decision No.: 329936
Petition No.: None
Assessment Type: Response to Comment
TXR No.: 0054713, 007306
MRID No.: None

DP Barcode: D292291
Registration No.: NA
Regulatory Action: Reregistration
Reregistration Case No.: NA
CAS No.: 7696-12-0
40 CFR: NA

FROM: Becky Daiss, Biologist
Risk Assessment Branch IV
Health Effects Division (7509P)

THROUGH: Susan Hummel, Branch Senior Scientist
Risk Assessment Branch IV
Health Effects Division (7509P)

TO: Monica Wait
Risk Manager Reviewer
Reregistration Branch 3
Pesticide Reevaluation Division (7508P)

This provides the Health Effects Division's (HED) evaluation of Valent BioSciences Corporation's supplemental report on derivation of a short-term oral benchmark dose (BMD) as an alternative to the No Observed Adverse Effect Level (NOAEL) used in previous tetramethrin assessments to derive short-term residential Margins of Exposure (MOEs) for hand to mouth activities. Based on HED's review, the BMD analysis as submitted is incomplete and inadequately documented. Analysis of additional effects that occurred at the LOAEL is required. Also, additional information on the effects modeled is required. More detailed comments on the submitted study are provided below.

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As noted in guidance for conducting and documenting BMD analysis, all effects observed at the LOAEL should either be modeled or a clear and adequate rationale for excluding specific effects from quantitative analysis should be provided. A separate BMD calculation should be conducted for each endpoint/study combination that is a reasonable candidate for becoming the basis for a final quantitative risk estimate. Unlike comparing NOAELs or LOAELs across endpoints or studies, the relative values of potential BMDs are not readily transparent until after the modeling has been completed. BMD guidance notes that typically, all endpoints within a study that the risk assessor has judged to be appropriate and relevant to the exposure should be considered for modeling. This will help ensure that no endpoints with the potential of having the lowest BMDL are excluded from the analysis. The apparent relative sensitivities of endpoints based on NOAELs/LOAELs may not correspond to the same relative sensitivities based on BMDs or BMDLs after BMD modeling; therefore, relative sensitivities of endpoints cannot necessarily be judged *a priori*.

In the submitted analysis, BMDs and BMDLs were calculated for mean maternal body weight on gestational and lactational days 20 in the F0 and F1 generation and for mean offspring body weight on day 21 in males and females in the F0F1 and F1F2 generation. As indicated in the attached Data Evaluation Record (DER) however, statistically significant body weight decreases were observed for both parent and offspring at a number other intervals (e.g., the mean body weight of the high-dose females during the F0 and F1 lactation periods were significantly decreased at days 1, 4, 7, 14 and 21). Given varying levels of percent decrease in body weight at different time intervals, BMD analysis of effects at additional earlier intervals for both pups and parental animals should be conducted.

In the submitted analysis, BMD/BMDLs were calculated using linear and polynomial models. BMD models typically used for continuous data include linear and polynomial models, and power models or other nonlinear models such as Hill models. Accordingly, the submission should either include additional BMD analysis using available alternative models or provide a rationale for limiting the analysis to use of the linear and polynomial models only.

Finally, statistical goodness-of-fit data generated by the BMD software (e.g., P-Value, AIC) were not provided in the submitted report. Reporting requirements for documentation of BMD modeling results are also provided in BMD guidance documents. As noted in the guidance, it is important to include goodness-of-fit test statistics in addition to graphic outputs for each case for any computation of a BMD or BMDL. Assessing goodness of fit (typically using a value of α=0.1) is critical to determining whether to accept or reject model results as a basis for POD computation. In cases where a number of models meet the recommended default statistical criteria for adequacy and visually fit, any of them theoretically could be used for determining the BMDL. In those cases, if the BMDL estimates from different models are sufficiently close, AIC results may be useful in identifying the model that provides the best fit and selecting the most appropriate BMDL for the POD.

Attachment

Tetramethrin Two Generation Rat Reproduction Study DER (TXR 007306, W. Dykstra, 6/30/89)

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

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JUN 30 1989

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Tetramethrin (Neopynamin) - EPA Registration No. 10308-01 - Two-Generation Rat Reproduction Study with Neopynamin Forte and UDS Mutagenicity Assay with Neopynamin

Caswell No.: 844
Project No.: 9-1400
Record No.: 244,785
MRID Nos.: 407778-01; 407784-01

FROM: William Dykstra, Reviewer
Review Section I
Toxicology Branch I - Insecticide, Rodenticide Support
Health Effects Division (H7509C)

TO: Paul Schroeder, PM Team 17
Insecticide-Rodenticide Branch
Registration Division (H7505C)

THRU: Robert Zendzian, Acting Section Head
Review Section I
Toxicology Branch I - Insecticide, Rodenticide Support
Health Effects Division (H7509C)

E.R. 6/23/89

Requested Action

Review rat reproduction study with Neopynamin Forte and UDS mutagenicity assay with Neopynamin.

Conclusion and Recommendation

1. The two-generation rat reproduction study with Neopynamin Forte is acceptable as Core-Minimum data and fulfills the data requirement for a rat reproduction study with Neopynamin.

2. The UDS mutagenicity assay is acceptable.

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Reviewed By: William Dykstra 6/21/89
Section I, Toxicology Branch I - IRS (H7509C)
Secondary Reviewer: Robert Zendzian, 6/21/89
Section I, Toxicology Branch I - IRS (H7509C)

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DATA EVALUATION REPORT

Study Type: 83-4 - Reproduction, Rat TOX Chem No.: 844

Accession No.: N/A MRID No.: 407778-01

Test Material: Neopynamin Forte

Synonyms: N/A

Study Number(s): HLA 343-~~174~~ 147

Sponsor: Sumitomo Chemical Company, Ltd.

Testing Facility: Hazleton Labs, Vienna, VA

Title of Report: Two-Generation Reproduction Study in Rats with Neopynamin Forte. IT-61-0201.

Authors: D.H. Pence, et al.

Report Issued: June 17, 1986

Conclusions:

The NOEL is 500 ppm, the mid-dose. At the LEL of 3000ppm, the high-dose, there were decreased body weights of males and females during the F_0 and F_1 growth phases, decreased food consumption of the F_0 females, decreased body weights of females during gestation and lactation of the F_0 and F_1 generation, decreased body weight of males and females during the 30-day postweaning period of the F_1 generation, decreased pup body weight in F_1 and F_2 litters, and increased incidence of bile duct hyperplasia of the liver in females of the F_1 parental animals.

Classification: Core-Minimum

Special Review Criteria (40 CFR 154.7): N/A

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Review:

Two-Generation Reproduction Study in Rats with Neopynamin Forte (IT-61-0201) (Hazleton Project No. HLA 343-174; June 17, 1986). Quality Assurance was performed and the report was signed by the QA officer.

A. Materials:

1. Test Material - Neopynamin Forte, Lot No. 00402, purity 93.4%, a viscous brown liquid.

2. Test Animals - Species: Rat; Strain: Sprague-Dawley; Age: 4 weeks; Weight: Males 156 to 214 g, females 126 to 164 g; Source: Charles River, Kingston, NY.

B. Study Design:

1. Randomized groups of 4-week-old male and female Sprague-Dawley albino rats were used in the study as the F_0 parental animals. The rats were assigned to the following groups:

Group	No. of Animals Male	No. of Animals Female	Dietary Level ppm
1 (Control)	13	26	0
2 (Low)	13	26	100
3 (Mid)	13	26	500
4 (High)	13	26	3000

Upon completion of weaning of the F_1 litters, 15 F_1 males and 30 F_1 females from each dietary group were randomly assigned to their respective groups to constitute the second generation parental animals.

2. Diet Preparation - Diet was prepared once each week and stored at room temperature. Samples of treated food were analyzed for stability and concentration at weeks 1, 2, 3, and 4 and once every 4 weeks thereafter.

Results - Results of diet analyses showed that the test material was stable for 7 days and was homogeneously distributed in the diet. Routine concentration analyses performed at specified intervals ranged from 82.8 to 116.4 percent of selected levels.

3. Animals received food (Purina Rodent Laboratory Chow®) and water ad libitum.

4. Statistics - Statistical evaluations of the data were performed and were considered significant at $p < 0.05$.

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C. Methods and Results:

1. Observations - All animals were observed daily for toxic signs and mortality.

Results - Seven parental animals were found dead or sacrificed in extremis. There were one mid-dose male and one high-dose female F_0, and one control female, two low-dose male, and two high-dose female F_1 rats. Gross necropsy findings of these animals did not reveal any compound-related effects and the deaths were not attributed to treatment. Clinical observations which were observed more frequently in compound-treated groups in comparison to controls for parental F_0 and F_1 animals were alopecia, urine-stained fur, thinness, hunched appearance, rough hair coat, and rhinnorrhea. These findings were not strictly dose-related and the toxicological significance, therefore, is uncertain.

2. Body Weight - Body weight was measured weekly for the F_0 and F_1 parental rats.

Results - Mean body weights of F_0 male and female animals of the mid- and high-dose groups were about 3 to 8 percent decreased during the growth period. At growth week 15, high-dose female F_0 body weight was 8 percent less than controls and was statistically significantly decreased.

In the F_1 growth period, mean body weight of the high-dose males and females was 7 to 10 percent decreased during growth. At week 18 of the F_1 growth period, body weight of high-dose females was 10 percent less than controls and was statistically significantly decreased.

Mean body weights of high-dose females during the F_0 and F_1 gestation periods were significantly decreased at days 0, 7, 14, and 20. Similarly, mean body weights of the high-dose females during the F_0 and F_1 lactation periods were significantly decreased at days 1, 4, 7, 14, and 21.

Mean body weights of mid- and high-dose males of the F_0 generation and high-dose males of the F_1 generation were decreased (4 to 6%) during the postmating phases in comparison to controls. The mean body weight of the low-dose males was significantly increased at week 25 in the F_1 postmating phase.

During the 30-day postweaning F_1 period, mean body weights of high-dose males and females were decreased (6% for males and 11% for females) in comparison to controls. Low-dose males during the F_1 postweaning period continued to exceed controls in body weight.

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3. Food Consumption - Food consumption was determined weekly.

Results - Food consumption was decreased by 7 percent for high-dose females during weeks 6 to 15 of the F_0 growth phase. Food consumption of F_0 males and F_1 males and females was comparable between control and treated groups.

4. Evaluation of Mating and Reproductive Indices - Analysis of the mating and reproductive indices were performed for each generation.

Results - Gestation length in days was between 22.1 and 22.3 for the F_0 females and 22.3 and 22.4 for the F_1 females. There was no compound-related effect on gestation length.

With respect to reproduction indices and offspring survival data, there were no compound-related effects in the F_1 or the F_2 generations. There were no compound-related effects in female fertility rate, male fertility rate, or gestation index. Offspring survival indices were unaffected by treatment in the F_1 and F_2 litters.

In the F_1 litters, mean offspring body weight at the high-dose was significantly decreased in male and female pups at days 14 and 21 of weaning. These data are shown below.

F_0 Generation (F_1 Litters)

Mean Pup Body Weight (grams)	Group	1	2	3	4
	Dose (ppm)	0	100	500	3000
Males at Day 14		24.2	25.1	25.2	21.7*
Females at Day 14		22.9	24.3	23.6	20.6*
Males at Day 21		36.5	37.0	38.2	32.0*
Females at Day 21		34.8	36.6	35.9	30.3*

* $p < 0.05$

Similarly, in the F_2 litters, mean offspring body weight at the high-dose was significantly decreased in

males at day 7, males and females at day 14, and males at day 21. These data are shown below:

F_1 Generation (F_2 Litters)

Mean Pup Body Weight (grams)	Group Dose (ppm)	1 0	2 100	3 500	4 3000
Males at Day 7		13.1	12.5	13.3	11.0*
Females at Day 7		12.3	11.9	12.5	10.7
Males at Day 14		25.7	25.1	26.7	21.0*
Females at Day 14		24.6	24.2	25.4	20.8*
Males at Day 21		39.4	38.3	41.5	32.3*
Females at Day 21		37.5	36.9	39.2	32.5

*$p < 0.05$

5. Sacrifice and Pathology - After the last F_1 litter was weaned, all surviving F_0 males and females were sacrificed, necropsied, and discarded. Gross observations were recorded.

After the last F_2 litter was weaned, F_1 animals continued to receive the appropriate diets for 30 additional days when 10 males and 25 females per group were randomly selected for gross and histopathological evaluation. All remaining F_1 animals were sacrificed, necropsied, and discarded. Gross observations were recorded.

In addition, five weanlings/sex/group from the F_1 and F_2 generations were selected randomly for gross necropsy and histopathologic evaluation. All remaining pups were sacrificed, necropsied, and discarded. Gross observations were recorded.

The following tissues from each animal selected for histopathological evaluation were preserved in 10% neutral buffered formalin, embedded in Paraplast, sectioned, stained with hematoxylin and eosin, and examined microscopically:

- Brain
- Pituitary
- Thoracic spinal cord
- Lumbar spinal cord
- Eyes
- Duodenum, jejunum, ileum
- Colon, cecum
- Mesenteric lymph node
- Urinary bladder
- Testes with epididymides

Mandibular salivary glands	Prostate
Thyroid	Ovaries
	Uterus
Trachea	Femur
Thymus	Femoral bone marrow smear
Esophagus	Lung[a]
Heart	Liver[b]
Spleen	Kidneys
Adrenals	Stomach
Pancreas	Lesions

[a]Two sections examined microscopically.
[b]Two lobes examined microscopically.

Results - Gross pathology findings of F_0 males and females that were sacrificed after weaning of the F_1 offspring and F_1 parental animals sacrificed after the 30-day feeding period following weaning of the F_2 offspring did not show any compound-related effects.

Histopathological evaluation of the tissues showed a possible compound-related increase in bile duct hyperplasia in the liver of F_1 female high-dose rats, characterized by minimal to slight proliferation of bile duct and ductile cells.

The incidence of this lesion is shown below:

	Female F_1 Parental Rats			
Group	Control	Low	Mid	High
No. examined	25	25	25	25
Liver				
Bile Duct Hyperplasia	12	8	10	22

Clinical observation of offspring of the F_1 and F_2 litters showed an increased incidence of small and/or languid pups in high-dose F_2 litters in days 7, 14, and 21 in comparison to controls.

Evaluation of gross and microscopic observations of pups in the F_1 and F_2 litters did not reveal any compound-related lesions.

Reviewed By: William Dykstra
Section I, Toxicology Branch I - IRS (H7509C)
Secondary Reviewer: Robert Zendzian
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DATA EVALUATION REPORT

Study Type: 84-2 - Mutagenicity

TOX Chem No.: 844

Accession No.: N/A

MRID No.: 407784-01

Test Material: Neopynamin

Synonyms: Tetramethrin

Study Number(s): 1280

Sponsor: Sumitomo Chemical Company, Ltd.

Testing Facility: Takarazuka Research Center, Osaka, Japan

Title of Report: In Vitro Unscheduled DNA Synthesis (UDS) Assay of Neopynamin in Rat Hepatocytes. IT-80-0213

Author: S. Kogiso

Report Issued: June 30, 1988

Conclusions:

Hepatocytes were isolated from young male Sprague-Dawley rats and exposed for 20 hours to Neopynamin at six concentrations ranging from 0.2 to 100 ug/mL. The HDT was cytotoxic and formed a precipitate. Neopyramin was negative for mutagenic potential measured as induction of DNA-damage/repair. The positive control, 2-AAF, responded appropriately by inducing significant increases in both mean net grain counts (>10) and in the percentage of cells in repair (>75%).

Classification: Acceptable

Special Review Criteria (40 CFR 154.7): N/A

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Review:

In Vitro Unscheduled DNA Synthesis (UDS) Assay of Neopynamin in Rat Hepatocytes (Takarazuka Research Center Study No. 1280, June30, 1988).

A. Materials:

1. The test compound was Neopynamin, Lot No. 60210, purity 94.0%; dissolved in DMSO.

2. Positive Control - 2-Acetylaminofluorene (2-AAF) dissolved in DMSO.

Animals - Five- and 6-week-old male rats of Sprague-Dawley strain were obtained from Charles River Japan, Inc. The diet (CE-2, Clea Japan, Inc.) and water were provided ad libitum. The rats were acclimatized and quarantined for a week. Seven- and 8-week-old male Sprague-Dawley rats weighing 282 to 328 g were used for the study.

Methods - Rat hepatocytes were isolated from 7- to 8-week-old male Sprague-Dawley rats following standard procedures by in situ perfusion with collagenase.

To determine dose levels of Neopynamin in the UDS assay, a preliminary cytotoxicity test was conducted at concentrations of 3, 10, 30, 100, and 300 ug/mL.

In the UDS assay, the isolated hepatocytes were exposed for 20hours to Neopynamin at concentrations of 0.2, 1, 5, 25, 50, and 100 ug/mL. The test with the same cell population was conducted in duplicate for each dose and performed twice with different cell populations from different rats.

All slides were coded and analyzed in a blind manner. A net nuclear grain count was calculated by subtracting the highest count in background areas adjacent to the nucleus from a nuclear grain count. Fifty cells were analyzed for each test.

A two-way analysis of variance was used for net grain counts between Neopynamin-treated groups or positive control groups and the vehicle control group. Chi-square was used for the number of cells in repair in 100 cells observed.

Results - In the preliminary cytotoxicity test with Neopynamin, precipitates were observed at 30 ug/mL and above and cytotoxicity was observed at 100 and 300 ug/mL.

Therefore, the 100ug/mL dose was selected for the UDS assay as the highest dose. In the UDS assay, the mean net grain counts in the Neopynamin-treated groups ranged from -5.09 to -8.81 in Test I, and from -5.98 to -7.81 in Test II. These results were not different from the solvent controls which were -5.84 and -8.46 in Tests I and II, respectively.

Additionally, there was no significant difference between the vehicle control and Neopynamin-treated cells with respect to the number of cells having more than 5 net grain counts (cells in repair).

The positive control, 2-AAF, responded appropriately by inducing significant increases in both mean net grain counts (more than 10) and percentage of cells in repair (greater than 75%).

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57205:I:Dykstra:C.Disk:KENCO:05/27/89:de:gj:vo:ek:de:vo:de
R:57207:Dykstra:C.Disk:KENCO:06/01/89:DD:ek:rw

END

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Chemical Name: Tetramethrin

PC Code: 069003
HED File Code: 12000 Exposure Reviews
Memo Date: 10/8/2009
File ID: 00000000
Accession #: 000-00-0130

HED Records Reference Center
10/15/2009